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(54) Substance or composition for treatment of pregnancy-induced hypertension

(57) A substance or composition for combatting pregnancy-induced hypertension comprises as an active ingredient a pharmaceutically effective and acceptable amount of eicosapentaenoic acid or its pharmaceutically acceptable salts or derivatives containing the eicosapentaonate group.

SPECIFICATION

Substance or composition for treatment of pregnancy-induced hypertension

THIS INVENTION relates to the treatment and/or prophylaxis in mammals of pregnancy-induced hypertension. More particularly, the invention relates to a substance or composition for use in a method of treatment of the human or animal body by therapy or prophylaxis practised on said body for combatting pregnancy-induced hypertension; and to a method of treatment of the human body by therapy or prophylaxis practised on the human or animal body for combatting pregnancy-induced hypertension in the human body.

According to the invention there is provided a substance or composition for use in a method of treatment of the human or animal body by therapy or prophylaxis practised on the human or animal body for combatting pregnancy-induced hypertension, the substance or composition comprising as an active ingredient a pharmaceutically effective and acceptable amount of eicosapentaenoic acid or its pharmaceutically acceptable salts or derivatives containing the eicosapentaenoate group.

By pregnancy-induced hypertension is meant hypertension or elevated blood pressure in the female mammal body which, prior to its first pregnancy, has had no history indicating any predisposition to hypertension, the hypertension mainfesting itself after the onset of pregnancy and disappearing after termination of pregnancy. Such hypertension is frequently indicative of a predisposition to pre-eclampsia and is frequently associated with an abnormal sensitivity to vascular pressors.

The eisocapentaenoic acid may be in naturally occurring form. Thus, it may be in the form as encountered in fish oil such as anchovy oil, typically as hydroxyl group substituent on a triglyceride.

The active ingredient may thus be a triglyceride, at least one of whose hydroxyl groups is substituted by an eicosapentaenoate group, and the substance or composition may comprise a fish oil. Sufficient of the hydroxyl groups of the triglyceride may be substituted by eicosapentaenoate groups for the eicosapentaenoate groups to form about 25–30% by mass of the substance or composition. Certain selected naturally occuring fish oils can contain up to 30% by mass or more eicosapentaenoate groups, bearing in mind that the substituted triglycerides in question will typically have other hydroxyl group substituents thereon, eg other fatty acid groups.

Instead, the eicosapentaenoic acid may be present in a semi-synthetic form, eg in the ester form, derived from the triglyceride form, such as the ethyl ester thereof. In this case, after conversion of the triglyceride form from fish oil into the ethyl ester form, eicosapentaenoic acid concentrations of up to 98% by mass are obtainable. However, such high concentrations may be expensive, in which case, after esterification to the ethyl ester, refining up to a concentration of no more than 80% in a pharmaceutically acceptable solvent may be desirable.

The active ingredient may thus be an alkyl ester of eicosapentaenoic acid. The alkyl group of the ester may have at most 5 carbon atoms, and the active ingredient is conveniently the ethyl ester of eicosapentaenoic acid. When the active ingredient is an alkyl ester, the eicosapentaenoate groups may form 60–80% by mass thereof, the ester being dissolved in a pharmaceutically acceptable solvent.

Instead the active ingredient may comprise a salt of eicosapentaenoic acid and the salt may have as its cation a member of the group comprising magnesium and zinc.

In fish oils particularly, eicosapentaneonate groups are frequently encountered in the presence of docosahexaenoate groups, which may contribute to the activity of the eicosapentaenoate groups in combatting pregnancy-induced hypertension.

The substance or composition may thus include, in addition to the eicospentaenoate active ingredient, a pharmaceutically effective and acceptable amount of docosahexaenoic acid or its pharmaceutically acceptable salts or derivatives containing the docosahexaenoate group.

The eicosapentaenoate groups and the docosahexaenoate groups may together form 28–35% by mass thereof. The proportion of docosahexaenoate groups by mass will typically be lower than that of the eicosapentaenoate groups, the higher the proportion of the one, the lower the proportion of the other, and vice versa.

It follows that when a refined source of eicosapentaenoate group is employed, they may be associated with docosahexaenoate groups in the same proportions as are present in the raw material such as fish oil, the docosahexaenoate groups being refined eg by esterification of triglycerides from fish oil on which they form hydroxyl group substituents, in an essentially similar fashion, and simultaneously with the refining of the eicosapentaenoate groups.

The substance or composition in accordance with the invention will typically, as indicated above, be in the form of a naturally occurring substance such as a fish oil, or in the form of a solution of an eicosapentaenoic acid derivative, such as the ethyl ester thereof, in a pharmaceutically acceptable solvent, in unit dosage form in a capsule such as a soft gelatine capsule, the solvent, when used, acting as diluent.

The substance or composition may thus be in unit dosage form, and may be contained in a capsule.

Naturally, solid diluents may be used, in which case the substance or composition may be in the form of a tablet comprising solid diluent material with which the active ingredient is mixed. The composition or substance may instead be in the form of a syrup, or it may be in admixture with foodstuffs, beverages, or the like.

Each unit dosage may contain 2–4g of eicosapentaenoate groups.

The substance or composition may include an anti-oxidant, and the anti-oxidant may be selected from the group comprising Vitamin E and dodecyl gallate.

When Vitamin E is used, it may be used at levels of about 1–2% by mass of the active ingredient, and dodecyl gallate may be used at levels of about 50–100 parts per million by mass of the active ingredient. Gelatine encapsulation also resists oxidation.

When in unit dosage form, the dosage may be suitable eg for daily, twice-daily or thrice-daily administration. For an adult human of typically 50–100kg body weight, unit dosage for daily administration may, as indicated above, contain between 2,0 and 4,0g of active ingredient, ie the eicosapentaenoate groups.

Suitable solvents include plant oils, isotonic saline solutions or any other liquid or aqueous solvent which is pharmaceutically acceptable. As suggested above, the Applicant believes that the most convenient forms will in fact be fish oil, a fish oil concentrate or in a concentrated semi-synethetic form such as the ethyl ester, in a capsule.

Instead, the substance or composition may be in the form of an emulsion comprising water as its continuous phase, and, as its discontinuous phase, comprising said active ingredient, the active ingredient being selected from eicosapentaenoic acid, triglycerides at least one of whose hydroxyl groups is substituted by an eicosapentaenoate group, and alkyl esters of eicosapentaenoic acid.

This emulsion will be suitable for transfusion, typically for intravenous administration eg by drop infusion, and may contain a pharmaceutically acceptable emulsifier and/or one or more vegetable oils.

In a particular embodiment the emulsion may comprise a suitable pharmaceutically acceptable emulsifier and at least one vegetable oil, the active ingredient being selected from triglycerides from purified fish oils such as anchovy oil and the ethyl ester of eicosapentaenoic acid.

Such emulsions can, depending on the proportion of active ingredient therein which can vary within wide limits on a mass basis, be used to administer the active ingredient to a patient at dosage rates which can vary over a wide range, and can in principle be substantially higher than the highest oral dosage rates attainable.

In accordance with the invention the substance or composition will be employed for the treatment or prophylaxis of pregnancy-induced hypertension in pregnant women. This will typically be effected by administering the substance or composition in unit dosage form, eg daily, twice-daily or thrice-daily, in the dosages mentioned above.

Accordingly, the invention also extends to a method of treatment of the human or animal body by prophylaxis practised on the human body for combatting pregnancy-induced hypertension, which comprises administering thereto a substance or composition as described above.

For an adult of 50–100 kg body mass, the admnistration may be in unit dosage form on a daily, twice daily or thrice daily basis, at a dosage rate of 2–4 g/day of active ingredient.

Without being bound by theory, the Applicant believes that the utility of the eicosapentaenoic acid (or its derivatives or salts containing the eicosapentaenoate group) in the prevention or treatment of pregnancy-induced hypertension arises from its effect on the dynamic balance in the warm-blooded body between the production of prostacyclin and thromboxane, prostacyclin being a vaosdilator and thromboxane being a vasoconstrictor. As shift in this dynamic balance in favour of postacyclin tends to reduce pregnancy-induced hypertension, and evidence has been found that pregnancy-induced hypertension may be associated with reduced prostacyclin generation in women, with the shift of said dynamic balance in favour of thromboxane.

The broad scheme protaglandin synthesis involves the conversion of membrane phospholipids by phospholipase A_2 to arachidonic acid, and conversion of his arachidonic acid by cyclooxygenase to endoperoxides, which in turn are converted at the cellular level to prostacylin, thromboxane and other prostanoids.

In the metabolization at the cellular level of fatty acids from the circulating metabolic pool to prostaglandins, different fatty acids can compete with one another. Eicosapentaenoic acid, whether derived from alpha-linoleic acid, or whether administered directly, isa precursor for the so-called 3-series of prostaglandins, with a predeliction in favour of prostacyclin production. On the other hand, linoleic acid leads to the production of dihomo-gamma-linolenic acid and then to arrachidonic acid, and, ultimately, as mentioned above, to prosstacyclin and thromboxane, via the 1-series and 2-series of prostaglandins respectively. Arachidonic acid can also be obtained from red meat.

It is believed that eicosapentaenoic acid competes with a arachidonic acid for the cyclo-

oxygenase enxyme, leading to a reduced production of prostacyclin and thromboxane from arachidonic acid, and to an increased production of prostacyclin from the eicosapentaenoic acid, without the associated production of thromboxane.

It follows that the prostacyclin/thromboxane balance is disturbed, in favour of increased prostacylcin production and reduced thromboxane production, at the cellular level, resulting in increased vasodilator production and decreased vasoconstrictor production. This in turn reduces or prevents any sensitivity in the body undergoing treatment to vascular pressors, leading ultimately to the prevention or control of pregnancy-induced hypertension.

The use of the substance or composition of the invention will now be described, by way of example, with reference to the following non-limiting illustration Examples.

EXAMPLE 1

Two pregnant women suffering from pregnancy-induced hypertension were treated with the substance or composition of the invention in the form of a refined fish oil, containing eicosapentaenoate groups as triglyceride hydroxyl group substituents, said groups being present at a concentration of 28–35% by mass. The fish oil was administered in the form of capsules, each containing agent 0,16g of active ingredient expressed as eicosapentaenoate groups, the encapsulation being by means of soft gelatine and the fish oil containing slightly less than 100 parts per million dodecyl gallate as antioxidant. Each patient received the capsules three times a day, divided into roughly equal does, the daily dose being twenty capsules, giving 3,2g of active ingredient/day in total.

In each case the pregnancy, which would otherwise have been terminated, was permitted to be extended by the treatment for a period of about three weeks, after which a successful birth took place.

Results are set out in the following table, Table 1, from which it is apparent that blood pressure and hypertension were reduced from abnormally high levels to acceptable levels; no significant changes took place in creatinin clearance; there was a slight, but not unacceptable, increase in platelet counts in the blood; and urate levels in the blood were reduced. It was also noted that no changes were observed in liver function tests performed; and no undesirable side-effects were observed.

TABLE 1

	Patient A		Patient B	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Blood Pressure	150/100	130/90	155/101	130/90
Urate (milli moles/l)	0,42	0,38	0,43	0,38
Platelet count	160 000	200 000	180 000	210 000
Creatinin Clearance (ml/min)	120	120	120	119
Prolongation of Pregnancy (days)		21		19

EXAMPLES 2–5

In these Examples, four further pregnant women, all pregnant for the first time and suffering from pregnancy-induced hypertension and pre-eclampsia were treated with the fish oil referred to in Example 1 at the same dosage rate as in Example 1. In each case they were admitted as patients to hospital and were immediately subjected to bed rest and treatment with methyldopa (Alcomet) administered orally at a dosage rate of 250 mg doses administered every six hours.

EXAMPLE 2

The patient was 19 years old and admitted to hospital 30 weeks pregnant, with a blood

pressure level of 170/110 on admission, a platelet count of 150000 on admission, and a urate level of 0,41 millimoles/l on admission. Treatment with the fish oil started within five days of admission. The patient's blood pressure declined on bed rest and on starting the fish oil administration. After one week of fish oil administration the methyldopa treatment was stopped. The reduction in blood pressure was maintained thereafter, the platelet count having risen to 200000 and the urate level having fallen to 0,34 millimoles/l. Four weeks after admission, it was decided that the fetus was mature and the patient was successfully and electively induced.

EXAMPLE 3

In this case the patient was 20 years old and had a blood pressure of 160/105 upon admission. Within one week of commencement of fish oil administration, which started within 5 days of admission, blood pressure decreased and anti-hypertensive therapy by means of methyldopa was discontinued. After 10 days of treatment with fish oil, the platelet count of 200000 on admission had increased to 300000, and urate level had fallen from 0,39 millimoles/l to a value of 0,31 millimoles/l. The patient was successfully induced on an elective basis, three weeks after admission, as the fetus was judged to be mature.

EXAMPLE 4

In this case the patient was 24 years old and had a blood pressure of 180/120 on admission. Monohydralazine HCl (Apresoline) treatment at an oral dosage rate of 40 mg every 8 hours was commenced, together with the bed rest and methyldopanine treatment, immediately upon admission. Fish oil treatment was started within 5 days of admission. Effective reduction in blood pressure occurred within 14 days of starting the fish oil administration. Urate and platelet count values, which were 0,42 millimoles/l and 150000 respectively upon admission, changed after said 14 days to 0,29 millimoles/l and 250000. Five weeks after admission the fetus was judged to have reached pulmonary maturity, and the patient was successfully electively induced.

EXAMPLE 5

In this case the patient was 20 years old and was admitted 30 weeks after the start of pregnancy, with a blood pressure of 180/120, a urate level of 0,38 millimoles/l and a platelet count of 240000. Fish oil treatment was started within 5 days of admission. Fourteen days after fish oil treatment was started, an effective reduction in blood pressure was found to have taken place, without, however, any material change in urate level or platelet count. All antihypertensive treatment, except the fish oil, was stopped 21 days after fish oil administration was started. The patient fulminated four weeks after admission with a dramatic increase in blood pressure and proteinuria levels. Termination of pregnancy was judged necessary for material indications and the patient was successfully induced.

From the Examples it is apparent that the invention provides a substance or composition which acts to reduce pregnancy-induced hypertension, which is easily administered, and which appears to produce no undesirable side-effects. Although primarily intended for human use, there is no reason for the substance or composition not to be useful for the same purpose in any mammal, at the same dosage rate in terms of g/kg/day. Furthermore, from Examples 3 and 5 it appears that, at least for a limited period, antihypertensive treatment other than with fish oil can be discontinued, without an immediate increase in blood pressure.

CLAIMS

1. A substance or composition for use in a method of treatment of the human or animal body by therepy or prophylaxis practised on the human or animal body for combatting pregnancy-induced hypertension, the substance or composition comprising as an active ingredient a pharmaceutically effective and acceptable amount of eicosapentaenoic acid or its pharmaceutically acceptable salts or derivatives containing eicosapentaenoate group.

2. A substance or composition as claimed in claim 1, in which the active ingredient is a triglyceride, at least one of whose hydroxyl groups is substituted by eicosapentaenoate group.

3. A substance or composition as claimed in claim 2, which comprises a fish oil.

4. A substance or composition as claimed in claim 2 or claim 3, in which sufficient of the hydroxyl groups of the triglyceride are substituted by eicosapentaenoate groups for the eicosapentaenoate groups to form about 25–30% by mass of the substance or composition.

5. A substance or composition as claimed in claim 1, in which the active ingredient is an alkyl ester of eicosapentaenoic acid.

6. A substance or composition as claimed in claim 5, in which the alkyl group of the ester has at most 5 carbon atoms.

7. A substance or composition as claimed in claim 6, in which the active ingredient is the etyl ester of eicosapentaenoic acid.

8. A composition as claimed in any one of claims 5 to 7 inclusive, in which the eicosapentaenoate groups form 60–80% by mass thereof, the ester being dissolved in a pharmaceutically

acceptable solvent.

9. A substance or composition as claimed in claim 1, in which the active ingredient comprises a salt of eicosapentaenoic acid.

10. A substance or composition as claimed in claim 9, in which the salt has as its cation a member of the group comprising magnesium and zinc.

11. A substance or composition as claimed in any one of the preceding claims which includes, in addition to the eicosapentaenoate active ingredient, a pharmaceutically effective and acceptable amount of docosahexaenoic acid or its pharmaceutically acceptable salts or derivatives containing the docosahexaenoate group.

12. A substance or composition as claimed in claim 11, in which the eicosapentaenoate groups and the docosahexaenoate groups together form 28–35% by mass thereof.

13. A substance or composition as claimed in any one of the preceding claims, which is in unit dosage form.

14. A substance or composition as claimed in claim 13, which is contained in a capsule.

15. A substance or composition as claimed in claim 13, which is in the form of a tablet comprising solid diluent material with which the active ingredient is mixed.

16. A substance or composition as claimed in any one of claims 13 to 15 inclusive, in which each unit dosage contains 2–4g of eicosapentaenoate groups.

17. A substance or composition as claimed in any one of the preceding claims, which includes an anti-oxidant.

18. A substance or composition as claimed in claim 14, in which the anti-oxidant is selected from the group comprising Vitamin E and dodecyl gallate.

19. A substance or composition as claimed in claim 1, which is in the form of an emulsion comprising water as its continuous phase and, as its discontinuous phase comprising said active ingredient, the active ingredient being selected from eicosapentaenoic acid, triglycerides at least one of whose hydroxyl groups is substituted by an eicosapentaenoate group, and alkyl esters of eicosapentaenoic acid.

20. A substance or composition as claimed in claim 19, which comprises a suitable pharmaceutically acceptable emulsifier and at least one vegetable oil, the active ingredient being selected from triglycerides from purified fish oils and the ethyl ester of eicosapentaenoic acid.

21. A substance or composition for use in a method of treatment of the human or animal body by therapy or prophylaxis practised on the human or animal body for combatting pregnancy-induced hypertension, substantially as described herein.

22. A method of treatment of the human or animal body by prophylaxis practised on the human or animal body for combatting pregnancy-induced hypertension, which comprises administering thereto a substance or composition as claimed in any one of claims 1 to 21.

23. A method as claimed in claim 22, in which for an adult of 50–100 kg body mass, the administration is in unit dosage form on a daily, twice daily or thrice daily basis, at a dosage rate of 2–4 g/day of active ingredient.

24. A method of treating the human or animal body by prophylaxis practised on the human body for combatting pregnancy-induced hypertension, substantially as described herein.

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